Safely and Effectively Evaluating Computed Tomography–detected Lung Lesions

Much Work to Be Done

A. Cole Burks[1], Michael K. Gould[2]*, Gerard Silvestri[3], Lonny B. Yarmus[4], Catherine R. Sears[5], Douglas A. Arenberg[6], Anne V. Gonzalez[7], Christopher G. Slatore[8], Nichole T. Tanner[3], Anil Vachani[9], Patrick Nana-Sinkam[10], Mark M. Fuster[11], Momen M. Wahidi[12], Lynn T. Tanoue[13], and M. Patricia Rivera[1]

[1]Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [2]Department of Research and Evaluation, Kaiser Permanente–Southern California, Pasadena, California; [3]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; [4]Division of Pulmonary and Critical Care, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; [5]Division of Pulmonary Medicine, Department of Medicine, Indiana University, Indianapolis, Indiana; [6]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan at Ann Arbor, Ann Arbor, Michigan; [7]Division of Respiratory Medicine, Department of Medicine, McGill University, Montreal, Quebec, Canada; [8]Pulmonary and Critical Care Medicine, Department of Medicine, Oregon Health & Science University, VA Portland Health Care System, Portland, Oregon; [9]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [10]Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia; [11]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California, San Diego, San Diego, California; [12]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Duke University, Durham, North Carolina; and [13]Section of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, Yale University, New Haven, Connecticut

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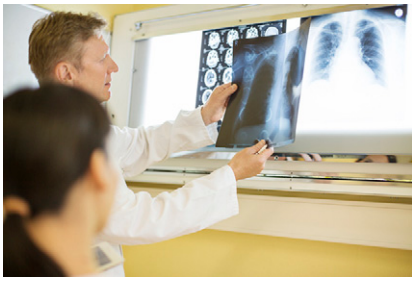

Despite advances in diagnosis and treatment, lung cancer remains the most common cause of cancer death in the United States and worldwide. Shifting the stage distribution at diagnosis from advanced to localized disease through lung cancer screening (LCS) reduces both lung cancer–specific and all-cause mortality, as demonstrated by the results of the National Lung Screening Trial (NLST) (1). LCS is a complex intervention that requires effective execution and coordination so that the benefits of screening outweigh the potential harms, including false-positive results and complications of downstream invasive testing. Because the real-world population eligible for LCS is likely to be older and to have more comorbidities than the participants enrolled in the NLST (2), there exists reasonable concern that patients undergoing LCS in the general population may experience more frequent complications. In this perspective, we discuss the burden of false-positive results of low-dose computed tomographic (LDCT) imaging of the chest and the effect of age and comorbidities on risk of procedural complications. We also discuss recent data on the complications and costs of invasive diagnostic pulmonary/thoracic procedures in the general population and how these data may relate to decision-making in regard to LCS and incidentally found lung abnormalities. Finally, we address systemic issues that likely contribute to the complication rate and advocate for effective communication within the patient/physician community to facilitate appropriate patient/procedure selection and risk–benefit discussions across the diagnostic spectrum of patients with potential lung cancer.

LCS has been shown to be effective in reducing mortality by 20% with LDCT

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Correspondence and requests for reprints should be addressed to A. Cole Burks, M.D., Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of North Carolina at Chapel Hill, 160 Dental Circle, CB 7219, Chapel Hill, NC 27599-7219. Email: acole_burks@med.unc.edu.

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compared with chest radiography in high-risk current and former smokers (1). However, this was associated with a high frequency of false-positive screening results and a small but not insignificant risk of complications related to downstream invasive testing. In the NLST, a considerably higher rate of positive screening results (defined as a noncalcified nodule measuring ⩾4 mm in average diameter) was noted in the LDCT group than in the radiography group (T0 [first screen], 27.3% vs. 9.2%; T1 [second screen], 27.9% vs. 6.2%; and T2 [third screen], 16.8% vs. 5.0%), and 96% of these participants did not have cancer (1). Of the 6,369 patients with positive LDCT results, 758 (11%) had invasive diagnostic testing (percutaneous needle, bronchoscopic, or surgical procedures). Of the 758 procedures, 295 (38.9%) were performed in patients with benign findings. Thus, 4.6% of the 6,369 patients with a positive LDCT result had an invasive procedure for benign disease (3). A *post hoc* analysis demonstrated that false-positive results were higher in older, Medicare-eligible (>65 yr old) patients, who were also more likely to undergo invasive diagnostic testing (2); however, the complication rate from invasive procedures appeared to be similar in both age group cohorts (4). This begs the question, At what point is the mortality benefit of screening outweighed by the morbidity and mortality of invasive workup?

With increased use of CT for both screening and diagnostic indications, the incidence of pulmonary nodules is also increasing. Approximately 9.1 million chest CT scans were performed in the United States in 2010, and that number continues to rise annually (5). Twenty percent to 30% (more than 2 million) of those scans will have an incidental finding requiring additional follow-up (6). As of 2015, only 4% of eligible patients in the United States underwent LCS, but if the entire eligible population—6.8 million people (7)—underwent screening, an estimated 1.6 million would have false-positive screening results (defined as any noncalcified nodule measuring ⩾4 mm, adenopathy, or pleural effusion later attributed to a benign etiology) (1). If one were to apply the Lung-RADS (Lung CT Screening Reporting and Data System) criteria for a positive screening result, defined as solid nodules of 6 mm or greater, the false-positive rate would decrease to 12.8%, which still results in nearly 1 million false-positive screening results (8). Although the majority of nodules requiring evaluation are incidentally detected, as LCS use increases, so will the number of CT-detected nodules and invasive diagnostic procedures performed to evaluate them. With an aging population, a larger burden of those procedures will likely be borne by older, less healthy patients with the comorbid conditions found with tobacco smoking and age, such as chronic obstructive pulmonary disease (COPD).

Unfortunately, every invasive diagnostic procedure carries a risk of complications, and COPD appears to increase that risk. Invasive procedures performed for lung abnormalities fall into three categories:

1. Needle based: either ultrasound-guided or CT-guided transthoracic needle aspiration;
2. Bronchoscopy based: including endobronchial ultrasound–guided, electromagnetic navigation with transbronchial needle aspiration, transbronchial biopsy, bronchoalveolar lavage, and transbronchial brushings; and
3. Surgery based: including thoracotomy, thoracoscopy, and mediastinoscopy.

In a population-based analysis, transthoracic needle aspiration was associated with an overall 16% complication rate, which was higher in current smokers, patients aged 60–69 years, and those with COPD (9). Bronchoscopic procedures for peripheral lung lesions have been associated with an overall complication rate of around 2% (10). In one study, the respiratory complication rates for bronchoscopy were higher in patients with COPD than in those patients without COPD (22% vs. 6%) (11). Likewise, outcomes of noncardiac thoracic surgery have been shown to be worse in patients with COPD, and patients with COPD are more likely to have other comorbidities (12). Considering that the NLST enrolled a highly selected, healthier cohort than the general screening population, and given that the study was conducted in high-volume, highly specialized centers, the ability to replicate the benefit/harm ratio of the NLST in community settings has been debated.

In fact, new data suggest that the risk of complications of invasive testing for pulmonary abnormalities may be higher in the general population than observed in the NLST (13). A recent study by Huo and colleagues estimated complications and costs of invasive diagnostic testing due to lung abnormalities on chest CT to be more than double those reported in the NLST (1, 13). The comparisons made with the NLST risk significant misinterpretation by suggesting that LCS itself, rather than evaluation of CT-detected abnormalities, in the general population results in higher rates of complications and downstream costs. However, the results of the study by Huo and colleagues are not necessarily generalizable to LCS. For example, their study cohort included patients in the same age range who underwent invasive diagnostic procedures similar to those performed in the NLST, but the procedures were for symptomatic or incidentally detected lung abnormalities; the clinical condition or indication for the procedures were not defined; and the patients may have been less healthy than their counterparts in the NLST. Therefore, the results should not be interpreted to imply that real-world LCS results in higher downstream complications and costs; rather, they should be considered as a global commentary on the medical community's limitations in managing CT-detected lung abnormalities (be they screen identified or incidental) across an aging and diverse patient population with a growing comorbidity burden. Such an observation, then, highlights the need to place significant importance on the process of correct selection of both the appropriate patient and procedure needed to best establish a diagnosis while exposing the patient to the least amount of harm.

The high rate of complications and costs associated with invasive diagnostic procedures in the general population observed by Huo and colleagues (13), as well as the increasing age and comorbidities of the U.S. population, also emphasizes the need for discussing potential harms and costs with all patients who are recommended to undergo diagnostic pulmonary procedures for CT-detected abnormalities. Pulmonary physicians must strive to offer LCS and the ensuing diagnostic procedures to those who would benefit most (i.e., those patients in whom the rising risk of lung cancer death outweighs the harms of pursuing diagnosis) (2). In addition, we must also be thoughtful and diligent in the way we develop programs: not only to screen for lung cancer but also to manage incidentally and symptomatically identified lung abnormalities.

Unfortunately, there remain substantial gaps between evidence-based,

guideline-directed care and the real-world medical experience. In 2014, Ost and colleagues demonstrated that, across all medical settings, only 21% of patients had a diagnostic evaluation for lung cancer consistent with guidelines, and smaller-volume centers tended to provide less guideline-consistent care than their high-volume counterparts (14). There is also an ever-growing body of literature suggesting that lung cancer care in high-volume programs or designated centers of excellence leads to better outcomes. For example, it has been suggested that general pulmonologists were less likely than interventional pulmonologists to perform guideline-appropriate endobronchial ultrasound staging (15). The surgical literature also suggests that outcomes are better when the surgeon performing the procedure is specialized in thoracic surgery and if the cancer care is delivered in a high-volume versus low-volume setting (15, 16). However, the vast majority of the U.S. population obtains care at low-volume centers, and the demand for subspecialized care far outstrips the supply.

The need for a comprehensive, multidisciplinary approach to abnormalities detected by chest CT remains critical to optimizing and individualizing diagnostic algorithms for each patient by minimizing futile procedures, maximizing diagnostic yield, and optimizing mortality benefit. Multiple resources exist to aid providers and centers in developing LCS programs and management of nodules detected on LDCT and include evidence-based, protocol-driven algorithms, such as the American College of Chest Physicians (ACCP) clinical practice guidelines for the diagnosis and management of lung nodules, an official policy statement from the American Thoracic Society (ATS)/ACCP on components and implementation of LDCT LCS programs, and the ATS/American Lung Association LCS guide website (17–20). However, the need remains for a clinical tool to identify patients who will benefit the most from invasive diagnostic procedures while minimizing harms. Such a tool would ideally include individualized patient characteristics based on epidemiological and genomic classifier data to create an objective ratio of risk of lung cancer death to risk of harm from procedural complications, as well as provide an easy-to-follow management protocol. Until such a tool exists, a multidisciplinary approach, combined with risk–benefit discussions with the patient and family, can facilitate the decision-making process to individualize and optimize management of CT-detected lung abnormalities and is an essential component of the standard of care. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
2 Rivera MP, Tanner NT, Silvestri GA, Detterbeck FC, Tammemägi MC, Young RP, *et al*.; American Thoracic Society Assembly on Thoracic Oncology. Incorporating coexisting chronic illness into decisions about patient selection for lung cancer screening: an official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2018;198:e3–e13.
3 National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;368:1980–1991.
4 Pinsky PF, Gierada DS, Hocking W, Patz EF Jr, Kramer BS. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. *Ann Intern Med* 2014;161:627–633.
5 Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, *et al*. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. *JAMA* 2012;307:2400–2409.
6 Gould MK, Tang T, Liu IL, Lee J, Zheng C, Danforth KN, *et al*. Recent trends in the identification of incidental pulmonary nodules. *Am J Respir Crit Care Med* 2015;192:1208–1214.
7 Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015. *JAMA Oncol* 2017;3:1278–1281.
8 Pinsky PF, Gierada DS, Black W, Munden R, Nath H, Aberle D, *et al*. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015;162:485–491.
9 Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Ann Intern Med* 2011;155:137–144.
10 Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, Diaz-Mendoza J, *et al*.; AQuIRE Bronchoscopy Registry. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions: results of the AQuIRE Registry. *Am J Respir Crit Care Med* 2016;193:68–77.
11 Bellinger CR, Khan I, Chatterjee AB, Haponik EF. Bronchoscopy safety in patients with chronic obstructive lung disease. *J Bronchology Interv Pulmonol* 2017;24:98–103.
12 Yoshimi K, Oh S, Suzuki K, Kodama Y, Sekiya M, Seyama K, *et al*. Impact of airflow limitation on comorbidities and postoperative complications in patients undergoing thoracic surgery: a retrospective observational study. *Ann Thorac Cardiovasc Surg* 2016;22:146–152.
13 Huo J, Xu Y, Sheu T, Volk RJ, Shih YT. Complication rates and downstream medical costs associated with invasive diagnostic procedures for lung abnormalities in the community setting. *JAMA Intern Med* 2019;179:324–332.
14 Ost DE, Niu J, Elting LS, Buchholz TA, Giordano SH. Determinants of practice patterns and quality gaps in lung cancer staging and diagnosis. *Chest* 2014;145:1097–1113.
15 Miller RJ, Mudambi L, Vial MR, Hernandez M, Eapen GA. Evaluation of appropriate mediastinal staging among endobronchial ultrasound bronchoscopists. *Ann Am Thorac Soc* 2017;14:1162–1168.
16 Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;345:181–188.
17 Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, *et al*. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl):e93S–e120S.
18 Wiener RS, Gould MK, Arenberg DA, Au DH, Fennig K, Lamb CR, *et al*.; ATS/ACCP Committee on Low-Dose CT Lung Cancer Screening in Clinical Practice. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *Am J Respir Crit Care Med* 2015;192:881–891.
19 Mazzone P, Powell CA, Arenberg D, Bach P, Detterbeck F, Gould MK, *et al*. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. *Chest* 2015;147:295–303.
20 American Thoracic Society; American Lung Association. Implementation guide for lung cancer screening. New York, New York: American Thoracic Society and Chicago, IL: American Lung Association; 2019 [updated 2018 Nov 1; accessed 2019 Jun 23]. Available from: https://www.lungcancerscreeningguide.org/.